Bromine-76-Metabromobenzylguanidine: A PET Radiotracer for Mapping Sympathetic Nerves of the Heart

Héric Valette, Christian Loc'h, Karine Mardon, Bernard Bendriem, Pascal Merlet, Chantal Fuseau, Sana Sabry, David Raffel, Bernard Mazière and André Syrota

Service Hospitalier Frédéric Joliot, DRIPP-CEA, Orsay, France

Iodine-123-metaiodobenzylguanidine (MIBG) is used to qualitatively assess heart innervation with single-photon emission computed tomography (SPECT). This approach is clinically useful in the prognostic evaluation of congestive heart failure. To improve quantification of uptake of the tracer using positron emission tomography (PET), we studied the characteristics of the bromoanalog of MIBG. Bromine-76-metabromobenzylguanidine (^{76}Br-MBBG) was prepared from a heteroisotopic exchange between radioactive bromine atoms (noncarrier-added (^{76}Br) $BrNH_4$) and the cold iodine atoms of the precursor metaiodobenzylguanidine. Biodistribution was studied in rats and PET cardiac imaging performed in dogs. Myocardial uptake was high and prolonged in both species (mean half-life in dogs: 580 min). In rats, myocardial uptake was inhibited by desipramine by 64%, whereas after pretreatment with 6-hydroxydopamine uptake was reduced by 84%. In dogs pretreated with 6-hydroxydopamine or with desipramine, a steep washout of the tracer occurred (mean half-life: 136 min and 118 min, respectively). The nonspecific uptake plus the passive neuronal diffusion of the tracer could be estimated at about 25%–30% of the total fixation. In dogs, analysis of unchanged ^{76}Br-MBBG in plasma showed that radiotracer metabolism was slow: 60 min after injection, 80% of the radioactivity was related to unchanged ^{76}Br-MBBG. These preliminary findings suggest that ^{76}Br-MBBG could be used to quantitatively assess adrenergic innervation in heart disease using PET. When combined with use of ^{11}C-CGP 12177, cardiac adrenergic neurotransmission can be assessed.

J Nucl Med 1993; 34:1739–1744

The assessment of cardiac sympathetic neuronal function in vivo requires complex, invasive procedures based on the analysis of norepinephrine (NE) kinetics. The guanethidine analog metaiodobenzylguanidine (MIBG) labeled with ^{131}I or ^{123}I is used for the scintigraphic diagnosis and treatment of pheochromocytomas and neuroblastomas (*1–3*). MIBG shares cellular transport and storage mechanisms with NE. Both MIBG and NE enter the neuronal cells through the same uptake-1 system, i.e., the amine pump (*4*), are stored into chromaffin granules (*5–7*) and secreted in response to acetylcholine (*8*). Both MIBG and NE also enter myocytes (uptake-2) and MIBG also enters the neuron through a passive pathway. MIBG is not a substrate for catechol-O-methyl transferase or for monoamine oxydase. These characteristics of MIBG have been defined by pharmacological studies (*8*). The compound also has been used to study sympathetic innervation of the heart in animals and humans (*9–13*). This approach is clinically useful in patients with congestive heart failure (*14*). However, single-photon emission tomography (SPECT) imaging only allows semiquantitative studies of cardiac innervation. To overcome problems such as attenuation correction, quantification and spatial resolution, extending the diagnostic applications of MIBG to PET cardiology, we studied the ^{76}Br-labeled analog of MIBG (^{76}Br-MBBG). The present experiments were undertaken to evaluate the ability of MBBG to assess cardiac adrenergic innervation function. The pharmacological characteristics of ^{76}Br-MBBG (in vitro studies in rats) were compared to those of ^{123}I-MIBG and ^{3}H-NE. PET cardiac imaging was performed in dogs for in vivo evaluation of the tracer.

MATERIALS AND METHODS

Synthesis of ^{76}Br-MBBG

Ammonium (^{76}Br) bromide was produced by irradiation of natural arsenic (1.8 g) with a beam of 30 MeV (^{3}He) ions. After a 15-hr delay to eliminate ^{75}Br (half-life: 1.6 hr), the target was dissolved in 40 ml of sulfuric acid (180°C). After being cooled at 50°C and oxydated with chromic acid (4.2 g, 12 ml water), the radioactive bromine was taken out with a nitrogen stream and trapped as bromide in 2 ml of ammonia (1 mol/liter) that was later taken to dryness. Ammonium (^{76}Br) bromide was then dissolved in 200 μl of water.

Using a Cu^+ assisted substitution reaction (*15,16*), ^{76}Br-MBBG was prepared from the iodinated analog MIBG. Briefly, a heteroisotopic exchange between the radioactive bromine atoms (no-carrier-added (^{76}Br) $BrNH_4$) and the cold iodine atoms of the precursor (3 μmol) was performed at 165°C for 40 min in a sealed vial in the presence of Cu(II) and an excess of reducing agents (gentisic acid, ascorbic acid, citric acid). The reaction mixture was then poured on a C-18 cartridge (SePak, Waters, Milford, MA),

Received Feb. 4, 1993; revision accepted May 25, 1993.
For correspondence contact: H. Valette, Service Hospitalier Frédéric Joliot, DRIPP-CEA, 4 Place du Général Leclerc, 91401 Orsay, France.

TABLE 1
Biodistribution of ^{76}Br-MBBG in Rats

	2 hr (n = 6)	4 hr (n = 6)	DMI (n = 6)	6-OH D (n = 6)
Heart	1.39 ± 0.12	1.07 ± 0.13	0.5 ± 0.02 (−64% ± 3%)	0.17 ± 0.02 (−84% ± 4%)
Right ventricle	0.76 ± 0.06	0.57 ± 0.1	0.23 ± 0.01	0.09 ± 0.01
Left ventricle	0.63 ± 0.06	0.65 ± 0.05	0.17 ± 0.01	0.077 ± 0.01
Lungs	0.19 ± 0.03	0.13 ± 0.01	0.07 ± 0.01	0.16 ± 0.02
Liver	0.13 ± 0.01	0.09 ± 0.02	—	—
Spleen	0.065 ± 0.01	0.19 ± 0.04	—	—
Kidney	0.065 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.06 ± 0.005
Muscle	0.12 ± 0.02	0.09 ± 0.02	0.07 ± 0.01	0.33 ± 0.09
Adrenal glands	0.38 ± 0.03	0.29 ± 0.03	0.23 ± 0.01	0.26 ± 0.02
Blood	0.020 ± 0.004	0.020 ± 0.002	0.070 ± 0.008	0.02 ± 0.001

Rats were killed 2 hr and 4 hr after injection of ^{76}Br-MBBG.
DMI was administered 2 hr before injection of ^{76}Br-MBBG and rats killed 4 hr later.
Values are expressed as mean ± s.d. of the %kg dose/g.
DMI = desipramine; 6-OH D = 6-hydroxydopamine.

allowing a separation of metahalogenobenzylguanidine derivatives from byproducts by means of specific elutions with mixtures of water and methanol (polar byproducts were eluted with water). Bromide-76-MBBG was separated from the iodo precursor by high-pressure liquid chromatography (HPLC) on a reverse-phase semipreparative column (C-18 μ-Bondapak, Waters, Milford, MA) and a 0.01 mole/liter NaH_2PO_4-CH_3CN (85–15) mobile phase. After evaporation of the HPLC eluate, the labeled compound was dissolved in saline and filtered on a 0.22-μm Millipore membrane (Millipore, Bedford, MA).

Biodistribution in Rats

Four different series of adult male Wistar rats (weight: 150–200 g) were injected with 0.6 MBq (0.03 nmole) of ^{76}Br-MBBG in the tail vein. Two series of six animals were used as controls (killed 2 or 4 hr after injection of the tracer). A third series (n = 6) was intraperitoneally preloaded with 10 mg/kg of desipramine (*17*) 2 hr before injection of ^{76}Br-MBBG. A fourth series (n = 6) was pretreated intraperitoneally with 6 hydroxydopamine (100 mg/kg twice a day on two consecutive days) 5 days before the tracer injection (*18*). Tissues of different organs (heart, lung, liver, kidney, adrenal glands, spleen, muscle) were rapidly removed, blotted, weighted and their radioactivity measured using a gamma well-counter. The ^{76}Br-MBBG tissue concentrations were expressed as %kg dose/g.

The same experiments were performed using ^{123}I-MIBG (0.6 MBq, specific activity: 9 MBq/mg, CIS-Bio International, Saclay, France) and ^{3}H-NE (0.6 MBq, specific activity: 1200 MBq/mole, Amersham France, Les Ulis). The purity of ^{123}I-MIBG was controlled by TLC (Merck, Darmstadt, Germany) before each experiment. Rats were killed 4 hr after injection of ^{123}I-MIBG or 10 min after injection of ^{3}H-NE.

PET Study in Dogs

Experimental Protocols. Ten female beagle dogs (mean weight: 12 kg) were anesthetized with pentobarbital, intubated and artificially respired. PET scans and arterial blood samples (femoral catheter) were obtained at intervals up to 4 hr after injection of 20–30 MBq (1–2 nmole) of ^{76}Br-MBBG. In two control dogs, tyramine (500 μg) was intravenously injected at the end of this first acquisition (195 min), and the acquisition of a second series of images (three 5-min scans, two 10-min scans) was started simultaneously. In two other control dogs, the tyramine infusion (15 μg/kg/min) began 130 min after the ^{76}Br-MBBG injection and was continued for the next 2 hr (*19*). Blood samples were taken for the measurement of unchanged ^{76}Br-MBBG in plasma.

Two dogs were intravenously denervated with 6-hydroxydopamine (50 mg/kg; (*20*)) 1 wk before the PET imaging. Two dogs were intraperitoneally pretreated with desipramine (10 mg/kg) 2 hr before PET imaging (*11*).

Data Acquisition and Processing. Myocardial PET images of radiotracer distribution in dogs (Fig. 1) were obtained using a human brain scanner (model CTI 953B/31; CTI PET Systems, Knoxville, TN) also suitable for cardiac imaging of small animals (*21,22*). This scanner allows simultaneous acquisition of 31 slices (3.37 mm apart) with an intrinsic spatial resolution of about 6 mm (FWHM). The recovery coefficient measured in phantom, including the effect of scattered radiation, is 0.67 for a 13-mm sphere (*23*) with a Hanning filter (frequency cutoff of 0.5 cycle/pixel). Reconstructed images had a resolution of 8.5 mm. Transmission scans were acquired for 15 min using three retractable ^{68}Ge rod sources.

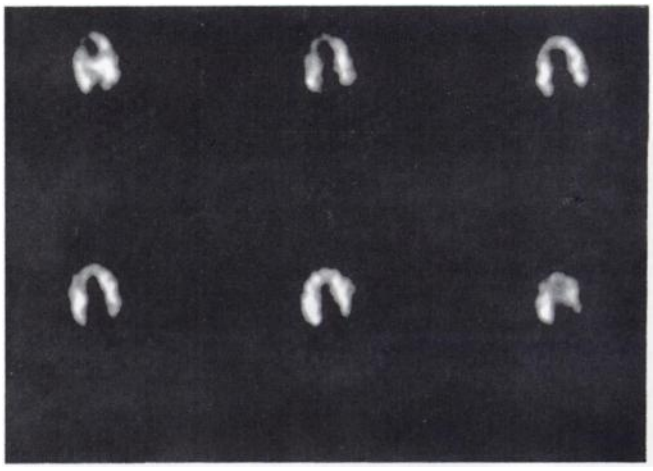

FIGURE 1. PET images of the canine heart. The panel shows the distribution of ^{76}Br-MBBG in six contiguous slices of the left ventricle of a normal dog 1 hr after injection of ^{76}Br-MBBG.

TABLE 2
Effect of Desipramine and 6-OH Dopamine on ^{76}Br-MBBG, ^{3}H-NE and ^{123}I-MIBG Heart Uptake

Heart uptake	Control (n = 6)	DMI (n = 6)	6-OH D (n = 6)
^{3}H-NE	0.98 ± 0.05	0.065 ± 0.013 (−93% ± 3%)	0.2 ± 0.02 (−80% ± 3%)
^{76}Br-MBBG	1.07 ± 0.13	0.5 ± 0.02 (−64% ± 3%)	0.17 ± 0.02 (−84% ± 4%)
^{123}I-MIBG	0.35 ± 0.03	0.2 ± 0.02 (−42% ± 4%)	0.21 ± 0.02 (−40% ± 2%)

Rats were killed 10 min after injection of ^{3}H-NE or 4 hr after injection of ^{123}I-MIBG or of ^{76}Br-MBBG.
DMI = desipramine; 6-OH D = 6-hydroxydopamine.
Values are expressed as mean ± s.d. of the %kg dose/g.

In four control dogs, imaging protocol was the following: twelve 10-sec scans, ten 1-min scans, ten 2-min scans, five 10-min scans and eight 20-min scans for a total data-acquisition time of 242 min. In six other dogs, the imaging protocol was three 5-min scans, two 10-min scans and eight 20-min scans for a total data-acquisition time of 195 min. The PET data were reconstructed using filtered backprojection and a Hanning filter with a cutoff frequency of 0.5 cycle per pixel. Global ^{76}Br-MBBG kinetics were determined by placing regions of interest (ROIs) over the left ventricular myocardium (usually a 70% isocontour) and the lungs.

Plasma Metabolite Study

The determination of unchanged ^{76}Br-MBBG in plasma (dogs) was performed by thin-layer chromatography (TLC) analysis. Plasma samples (0.2 ml) were deproteinized with methanol (2 ml) and centrifugated (1000 g). The supernatants were concentrated by evaporation, dissolved in 20 μl acetonitrile and the residues analyzed by TLC on ^{18}C plates (R_f of MBBG = 0.28; RP-$^{18}F_{254}S$, Merck, Darmstadt, Germany). After the migration, the distribution of the radioactivity on the plates was measured by a radiochromatogram analyzer (Berthold, Wildbad, Germany). The fraction of the unchanged radiotracer was then calculated as the ratio of the radioactive spot coinciding with ^{76}Br-MBBG to the total radioactivity of the strip.

RESULTS

Radiochemical Purity

The radiochemical yield and radiochemical purity were respectively 65% and > 98%. The specific activity, determined at the end of the preparation, was 10–20 MBq/nmole. Any presence of arsenic was checked (*24*) and found to be less than 6 ng.

Biodistribution and Pharmacological Interventions in Rats

The tissue concentrations of ^{76}Br-MBBG in rats are given in Table 1. The heart had the highest and most prolonged uptake; heart-to-lung ratio was eight 4 hr after injection of the tracer. The decrease of ^{76}Br-MBBG uptake after pretreatment with 6-OH dopamine was 84% ± 4%, while after pretreatment with desipramine it was 64% ± 3% (Table 2). After pretreatment with desipramine, reductions in myocardial uptake of ^{123}I-MIBG and of ^{3}H-NE were 42% ± 4% and 93% ± 3%, respectively (Table 2). In rats pretreated with 6-OH dopamine, reductions in ^{123}I-MIBG and ^{3}H-NE cardiac uptake were 40% ± 2% and 80% ± 3%, respectively (Table 2).

PET Studies

No change occurred in vital signs at any time during the study (except changes in heart rate and blood pressure during tyramine infusion). The average counts in the four heart slices in the two control dogs was: 98,500 ± 14,190 for the three 300-sec images, 185,440 ± 25,100 for the two 600-sec images and 278,060 ± 63,000 for the eight 1200-sec images (values are normalized for 37 MBq).

Myocardial uptake was high and prolonged (Fig. 2), whereas blood clearance was rapid (Fig. 3). The time course of the myocardium-to-lung ratio remains high (about 4–5) from the first 5 min and stable until the end of the experiment (Fig. 4). The ^{76}Br-MBBG slowly washed out (mean half-life = 580 ± 40 min; n = 4) from the myocardium.

Effects of Pharmacological Interventions. After injection of tyramine, the half-lives were 77 min (−85%) and 99 min (−81%) for the short (500 μg over 15 min; Fig. 5) and long infusions (15 μg/kg/min over 2 hr; Fig. 1) respectively. Reductions in ^{76}Br-MBBG heart content following injections of tyramine were 38% and 60%, respectively. In dogs pretreated with desipramine or with 6-OH dopamine, a steep washout of the tracer (half-life = 118 min, −77% and half-life = 136 min, −74%, respectively) was observed (Fig. 1).

Plasma Metabolite Study

For the measurement of unchanged ^{76}Br-MBBG in plasma, 91% of the radioactivity was recovered using protein elimination in methanol. In dogs, the metabolism of the radiotracer was slow: 87% and 80% of the radioactivity were related to unchanged ^{76}Br-MBBG respectively 30 min and 60 min after injection.

DISCUSSION

The present study shows that ^{76}Br-MBBG can be used as a reliable index of neuronal NE uptake and storage in the heart with PET.

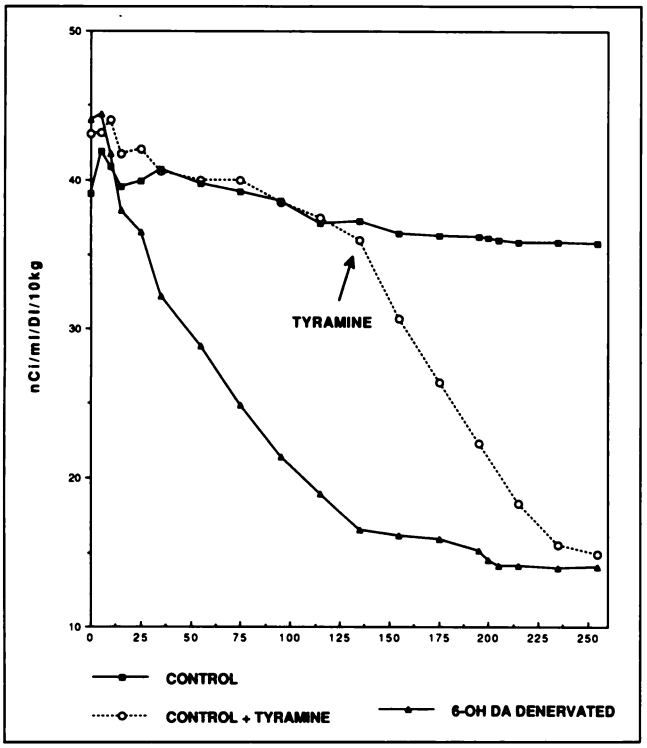

FIGURE 2. The figure shows the myocardial kinetics of ^{76}Br-MBBG in control dogs, in control dogs with tyramine long infusion and in dogs pretreated with 6-hydroxydopamine. Each curve is the mean value of two experiments. Values are normalized for 1 mCi and for 10 kg. The calculated mean half-life was 530 ± 45 min in control dogs.

In vitro Evaluation of Tracer Using Pharmacological Intervention

The data show that pharmacological treatment with desipramine, a drug known to alter the uptake-1 function of adrenergic nerves, significantly reduced the myocardial concentration of ^{76}Br-MBBG. This reduction appeared to be greater than that of ^{123}I-MIBG but less than that of ^{3}H-NE. The results with ^{123}I-MIBG or ^{3}H-NE are in accordance with previously published values reporting a 50% decrease in ^{125}I-MIBG uptake and a 94% decrease in ^{3}H-NE uptake (*11*). Reduction of ^{76}Br-MBBG uptake after 6-OH dopamine, a compound which selectively destroys sympathetic nerves endings, was similar to that of ^{3}H-NE, but significantly greater (*11*) than that observed with ^{125}I-MIBG or ^{123}I-MIBG (69%). These data suggest that the neuronal uptake of MBBG is less dependent on the passive diffusion uptake than that of MIBG. This may be due to the higher lipophilicity of the metaiodophenyl moiety compared with that of the metabromophenyl moiety. Therefore, despite the similarity of MIBG and MBBG, the present findings indicate that ^{76}Br-MBBG uptake is a better index of the cardiac uptake-1 function than MIBG. But the reduction in myocardial uptake of MBBG after desipramine or 6-OH dopamine is less important than that observed in rats with metaraminol derivatives such as 6-(^{18}F)-fluorometaraminol (*17,25*) or ^{11}C-hydroxyephedrine (*26*).

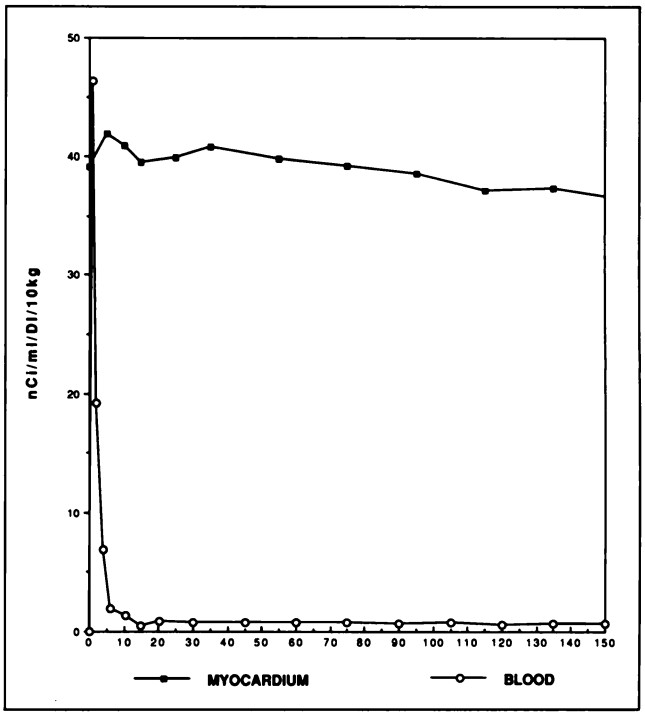

FIGURE 3. Myocardial and blood time activity curves in two control dogs. A plateau is rapidly observed in the myocardium while there is a rapid clearance from blood.

PET Evaluation of the Tracer

The data show that ^{76}Br-MBBG has prolonged cardiac retention and provides high quality images. This is an advantage for cardiac PET studies of neuronal NE uptake function. Similar findings were observed using ^{11}C-hydrox-

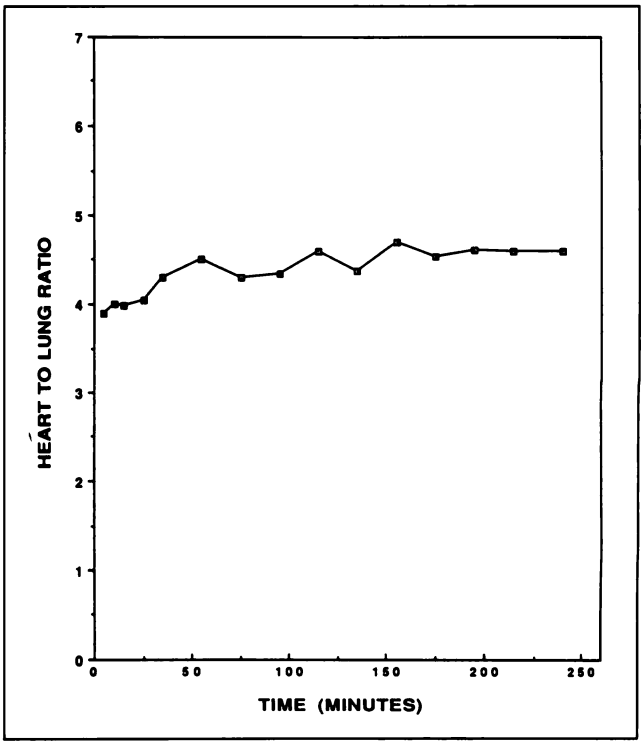

FIGURE 4. The heart-to-lung ratio is stable from 5 min after injection to the end of the experiment.

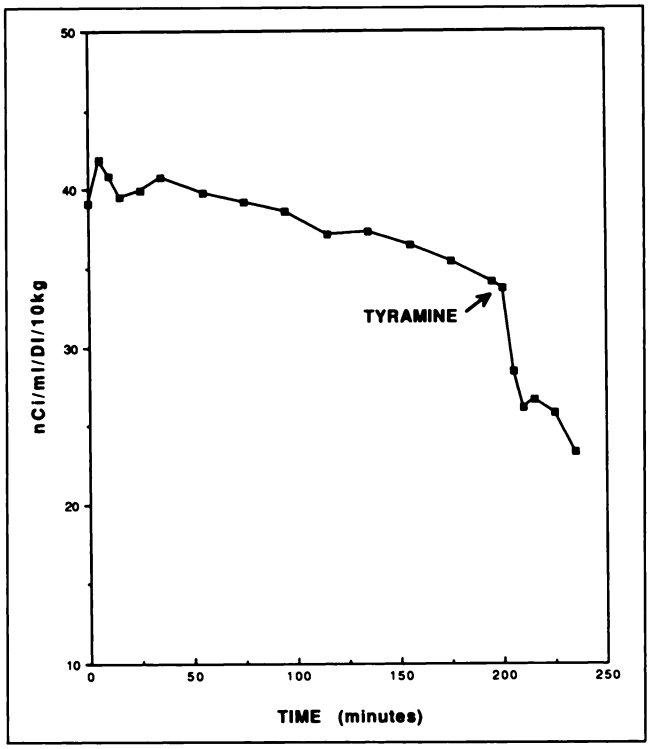

FIGURE 5. Effect of tyramine short infusion (500 μg) on MBBG myocardial content.

yephedrine (*26*) or 6-(^{18}F)fluoronorepinephrine (*27*). Images following the injection of the tracer are likely to be mainly flow-dependent since the initial uptake appears similar in control dogs and in 6-hydroxydopamine or desipramine pretreated dogs. Moreover, this indicates that there is significant nonspecific uptake within the first 2 hr after tracer injection in dogs. In vitro pharmacological experiments demonstrated that the proportion of nonspecific uptake of ^{76}Br-MBBG ranged between 25% and 30% in rats. This nonspecific uptake may represent the amount of extraneuronal uptake plus passive neuronal uptake. This value is higher than that observed with ^{18}F-fluorometaraminol or ^{11}C-hydroxyephedrine (10%), which suggests that metaraminol derivatives could be better indices of uptake-1 than norepinephrine itself (*28*). This value, observed in rats and dogs, does not preclude the use of ^{76}Br-MBBG in clinical studies, because the non-neuronal uptake mechanism does not appear to be significant in the human heart (*29*). In dogs, the amount of unmetabolized ^{76}Br-MBBG was similar (85%–75%) to that of ^{11}C hydroxyephedrine (*26*). For heart imaging in humans, radiation doses to the whole body have been estimated (*30*): i.e., from 20 mCi of ^{11}C-hydroxyephedrine = 0.186 rad; from 5 mCi of ^{123}I-MIBG = 0.27 rad; and from 0.5 mCi of ^{131}I-MIBG = 0.45 rad. The amount of ^{76}Br-MBBG can be estimated as 1 mCi; the corresponding radiation dose is 0.5 rad.

CONCLUSION

Bromine-76 is not a practical radionuclide because it cannot be obtained from all the cyclotrons. Its long half-life (16.2 hr) augments radiation exposure and restricts the administration dose. But, synthesis of ^{76}Br-MBBG is relatively simple. The specific activity at the end of the preparation is high. In spite of similarities between ^{123}I-MIBG and ^{76}Br-MBBG, the pharmacological data suggest that ^{76}Br-MBBG uptake is a better index of cardiac uptake-1 function than MIBG. The prolonged cardiac retention and long half-life of ^{76}Br provide an opportunity for evaluating the effects of pharmacological interventions on neuronal reuptake and release of the compound, at least for basic experiments. In humans, PET cardiac imaging of adrenergic neurotransmission pathways can be studied within one day: i.e., beta-adrenergic receptor density can be obtained early in the morning with ^{11}C-CGP 12177, and after the decay of ^{11}C, presynaptic sympathetic innervation can be assessed with ^{76}Br-MBBG.

REFERENCES

1. Wieland DM, Swanson DP, Brown LE, Beierwaltes WH. Imaging the adrenal medulla with an ^{131}I-labeled antiadrenergic agent. *J Nucl Med* 1979;20:155–158.
2. Wieland DM, Wu JL, Brown LE, Mangner TJ, Swanson DP, Beierwaltes WH. Radiolabeled adrenergic neuron blocking agents: adrenomedullary imaging with (^{123}I) iodobenzylguanidine. *J Nucl Med* 1980;21:349–353.
3. Gross M, Frager M, Valk T, et al. Localization of pheochromocytoma with I-131-M-iodobenzylguanidine [Abstract]. *J Nucl Med* 1981;22:5.
4. Jacques S, Jr, Tobes MC, Sisson JC. Comparison of the sodium dependency of uptake of metaiodobenzylguanidine and norepinephrine into cultured bovine adrenomedullary cells. *Mol Pharmacol* 1984;26:539–546.
5. Wieland DM, Brown LE, Les Roger W, et al. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 1981;22:22–31.
6. Nakajo M, Shimabukuro K, Yoshimuro H, et al. Iodine-123 metaiodobenzylguanidine intra- and extravesicular accumulation in the rat heart. *J Nucl Med* 1986;27:84–89.
7. Gasnier B, Roisin MP, Scherman D, Coornaert S, Desplanches G, Henry JP. Uptake of metaiodobenzylguanidine by bovine chromaffin granule membranes. *Mol Pharmacol* 1986;29:275–280.
8. Tobes MC, Jacques S, Wieland DM, Sisson JC. Effect of uptake one inhibitors on the uptake of norepinephrine and metaiodobenzylguanidine. *J Nucl Med* 1985;26:897–907.
9. Kline RC, Swanson DP, Wieland DM, et al. Myocardial imaging in man with I-123 metaiodobenzyl-guanidine. *J Nucl Med* 1981;21:129–132.
10. Stanton MS, Tuli MM, Radtke NL, et al. Regional sympathetic denervation after myocardial infarction in human detected noninvasively using I-123-metaiodobenzylguanidine. *J Am Coll Cardiol* 1989;14:1519–1526.
11. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jacques S. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 1987;28:1620–1624.
12. Sisson JC, Shapiro B, Meyers L, et al. Metaiodobenzylguanidine to map the adrenergic nervous system in man. *J Nucl Med* 1987;28:1624–1636.
13. Dae MW, O'Connel JW, Botvinick EH, et al. Scintigraphic assessment of regional cardiac adrenergic innervation. *Circulation* 1989;79:634–644.
14. Merlet P, Valette H, Dubois Randé JL, et al. Prognostic value of cardiac MIBG imaging in patients with congestive heart failure. *J Nucl Med* 1992; 33:471–477.
15. Mertens J, Vanryckeghem W, Bossuyt A. High yield preparation of ^{123}I-N-isopropyl-p-iodoamphetamine (IAMP) in presence of Cu(I). *J Lab Compd Radiopharm* 1985;22:89–91.
16. Moerlein SM, Hwang DR, Welch MJ. No carrier added radiobromination via cuprous chloride assisted nucleophilic aromatic bromodeiodination. *Appl Radiat Isot* 1988;38,5:369–372.
17. Mislankar SG, Gildersleeve DL, Wieland DM, Massin CC, Mulholland GK, Toorongian SA. 6-(^{18}F)Fluorometaraminol: a radiotracer for in vivo mapping of adrenergic nerves of the heart. *J Med Chem* 1988;31:362–366.
18. Yamada S, Yamamura HI, Roeske WR. Alterations in cardiac autonomic receptors following 6-hydroxydopamine treatment in rats. *Mol Pharmacol* 1980;18:185–192.
19. Goldstein DS, Chang PC, Eisenhofer G, et al. Positron emission tomo-

graphic imaging of cardiac sympathetic innervation and function. *Circulation* 1990;81:1606–1621.
20. Burks TF, Grubb MN, Peterson RG. Reduction of adverse acute cardiovascular actions of 6-hydroxydopamine in dogs by adrenergic receptor blockade. *Eur J Pharmacol* 1975;32:387–392.
21. Spinks TJ, Jones T, Bailey DL, et al. Physical performance of a new commercial positron tomograph with retractable septa. *IEEE Med Imaging Conf Rec* 1991;1313–1317.
22. Mazoyer B, Trebossen R, Deutch R, Casey M, Blohm K. Physical characteristics of the ECAT 953B/31: a new high resolution brain positron tomograph. *IEEE Trans Med Imaging* 1990;4:499–504.
23. Bendriem B, Trebossen R, Verrey B, et al. Quantitative evaluation of a new brain tomograph: the ECAT 953B/31 [Abstract]. *J Nucl Med* 1991;32,5: 1063.
24. Syrota A, Samson Y, Boullais C, et al. Tomographic mapping of brain intracellular pH and extracellular water space in stroke patients. *J Cereb Blood Flow Metab* 1985;5:258–368.
25. Wieland DM, Rosenpire KC, Hutchkins GD, et al. Neuronal mapping of the heart with 6-^{18}F-fluorometaraminol. *J Med Chem* 1990;33:956–964.
26. Rosenpire K, Haka MS, Van Dort ME, et al. Synthesis and preliminary evaluation of carbon-11-meta-hydroxyephedrine: a false transmitter agent for neuronal imaging. *J Nucl Med* 1990;31:1328–1334.
27. Ding Y-S, Fowler JS, Gatley SJ, Dewey SL, Wolf AP. Synthesis of high specific activity (+)- and (−)-6-(^{18}F)fluoronorepinephrine via the nucleophilic aromatic substitution reaction. *J Med Chem* 1991;34:767–771.
28. Herman W, Graefe KH. Relationship between uptake of ^{3}H-metaraminol and the density of adrenergic innervation in isolated rat tissues. *Arch Pharmacol* 1977;296:99–110.
29. Dae MW, De Marco T, Botvinick EH, et al. Scintigraphic assessment of MIBG uptake in globally denervated human and canine hearts. Implications for clinical studies. *J Nucl Med* 1992;33:1444–1450.
30. Shulkin BL, Wieland DM, Schwaiger M, et al. PET scanning with ^{11}C-hydroxyephedrine: an approach to the localization of pheochromocytoma. *J Nucl Med* 1992;33:1125–1131.